Generally, conservative management options should be exhausted prior to consideration of surgical intervention. Young patients with large defects present a potential exception to this recommendation, since lesion growth can occur even with symptomatic improvement from non-operative treatment, potentially worsening the structural problem. For example, the majority of young patients experience almost complete resolution of knee pain after removal of a loose osteochondritis dissecans (OCD) fragment. However, if the defect is left empty, 50% to 80% will develop radiographic evidence of osteoarthritis after 8 to10 years. This is the patient population where cartilage repair is deemed most beneficial, in hopes of slowing the progression of degenerative changes.

Cartilage damage encompasses a wide spectrum ranging from focal chondral defects all the way to tricompartmental osteoarthritis. While the latter is beyond the capabilities of current cartilage repair procedures, earlier stages in the disease process can be managed successfully with cartilage repair. Historically, attempts at cartilage repair tended to focus on the defect itself; often disregarding articular co-morbidities, such as malalignment or meniscal deficiency, that were the root cause for the development of cartilage damage in the first place. Not surprisingly, early reports of cartilage repair were disappointing; more recent studies, however, have shown success in over 70 to 80% of patients. This substantial improvement has been attributed to the increased recognition and treatment of articular co-morbidities concurrently with cartilage repair in a process termed biologic joint reconstruction.

Cartilage repair options are chosen depending on defect location and size. Generally, smaller defects (<2–3 cm^2) are amendable to minimally invasive procedures such as marrow stimulation and osteochondral autograft transfer (also known as OATS or Mosaicplasty). Larger defects have demonstrated disappointing outcomes with these procedures, and are therefore mostly treated with cell-based therapy utilizing autologous chondrocytes or osteochondral allograft transplantation. Several new implants are currently under development, and synthetic plugs have received increased attention in hopes of providing a cost-efficient, off-the shelf option.

However, careful attention is required to correctly identify and address the frequently present co-morbidities involved in the degenerative disease process, such as malalignment and meniscal deficiency. The concurrent use of osteotomy and meniscal transplantation is common and necessary to normalize the biomechanical environment.

I-15
EPIGENETICS: MARKS FOR FUTURE OA RESEARCH?

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Purpose: Osteoarthritis (OA) is a complex multifactorial disease. Several studies have suggested or identified epigenetic events, which include DNA methylation, histone modifications, and microRNAs, that may play a role in OA progression and the gene expression changes observed in diseased cartilage. Collectively epigenetic modifications allow the cell to respond quickly to environmental changes and these can be inherited during cell division. However, aberrant epigenetic modifications are associated with a number of pathological conditions, including OA. The aim of this talk is to inform about current research in epigenetics and epigenetics in OA. DNA methylation and chromatin changes in OA are currently understudied, with most work focussing on microRNAs which clearly have a role in skeletal development. Recent advancements in epigenetic research suggest that global analysis of such modifications in OA are now possible, however, with the exception of microRNAs, it will be a significant challenge to demonstrate how such modifications impact on the disease or how they could be readdressed to limit disease progression.

I-16
OSTEOARTHRITIS IS AN INFLAMMATORY DISEASE

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Osteoarthritis (OA) has long been considered as a “tear-and-wear” process. In the last 15 years, the face of OA has deeply changed, now considered as a disease involving all tissues of a joint eventually leading to cartilage degradation. Among these tissues, a particular attention has been recently paid on the role of synovium in the OA process. A patchy inflammation of this tissue is described, with some kind of correlation between the degree of the synovitis and the prognostic of the disease. Whether this synovitis is a primum movens of the process or secondary to a reaction to cartilage fragments falling into the joint remains debated. Many inflammatory mediators belonging to the cytokine family, to inflammatory lipid mediators, or to matrix components play a critical role in the OA process. Interestingly, the source of these soluble mediators may be the chondrocytes themselves (via autocrine/paracrine loops), the synovial cells and the subchondral bone cells. Interestingly, all the risk factors playing a role in OA have a potential to increase the release of inflammatory mediators into the joints (adipokines for obesity/metabolic syndrome, secretory profile of senescent chondrocytes, synovitis in post-trauma). The most recent studies highlight the possibility of cross-talks between joint cells leading to communication of mediators within and between the tissues of a joint. Finally, the paradigm based on a mechanical-driven origin of the disease is not conflictual with the inflammatory hypothesis since mechanical signals are shifted into biochemical signals in chondrocytes and subchondral bone cells via mechanoreceptors leading to the release of pro-degradative and pro-inflammatory mediators.

I-17
CHALLENGES IN STUDYING RISK FACTORS FOR OA PROGRESSION

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Purpose: While several risk factors have been indentified for incident radiographic knee osteoarthritis (ROA), findings on risk factors, especially chronic ones, for progression of ROA have been inconclusive. Some factors that increase the risk of incident knee ROA have an opposite effect on ROA progression. The reasons for such a paradoxical phenomenon have not been scrutinized. We explored several explanations that may underlie the discrepancy between findings for knee ROA progression and those for knee ROA incidence using causal diagrams and real data, when available. First, in observational studies of knee ROA progression conditioning on (or limiting to) subjects who already have mild or moderate disease will block the causal pathway between the risk factor of interest, which often occurs prior to the occurrence of ROA, and ROA progression; consequently it completely eliminates the effect of the risk factor on OA progression. Second, conditioning on preexisting disease will likely induce a negative correlation between the factor of interest and potential confounders; such bias tends to dilute effect estimates. Third, most studies of ROA progression often have followed participants over a long period of time. If a substantial proportion of subjects are lost to follow-up, the resulting selection bias can alter the effect estimate. Finally, knees that progress to end stage during the long interval between imaging assessments will be treated the same at the end of the study regardless of when they reached that stage; thus, the ceiling effects and the relatively insensitive measures used to assess ROA progression will make the effect estimate close to the null value. In conclusion, methodological challenges in observational studies of risk factors for ROA progression, especially chronic factors, are difficult to overcome. Novel study design and analytic approaches for ROA progression are required to address these issues.

I-18
WHAT MAKES CHONDROCYTES SPECIAL?

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Cartilage consists of a dense network of collagen fibres embedded in an aggrecan gel, within which is a sparse population of cells, the chondrocytes. Cartilage is tough and resilient and the matrix is dense and does not allow migration or trafficking of cells. The collagen and aggrecan are of extremely slow turnover and the load bearing properties of cartilage depend on its physical integrity and cohesive structure. Chondrocytes thus live within a special environment, which they are responsible for assembling during development and maintaining throughout life. Chondrocytes in adult cartilage thus lead a lonely existence over many decades and the ageing of chondrocytes may be a significant factor in chondrocyte biology and pathology.

Cartilage chondrocytes are needed throughout life to make, repair and remodel matrix. To carry out this function chondrocyte respond to a whole range of physical and biochemical signals that guide the balance of their activities. This includes paracrine and autocrine effects of growth factors, cytokines and chemokines and the biomechanical signals from tensile and compressive loading acting through cell matrix interactions and accompanying ionic and osmotic fluxes. These processes require the co-ordinated activity of many different pathways